

# The Genetic Centers of America

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Documents Management Division  
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Room 1061  
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October 25, 2004

**RE: FDA Docket #2004P-0349**

To Whom It May Concern:

These comments are being submitted in support of the Citizen Petition dated July 30, 2004, filed by Coalition for Mercury-Free Drugs with the FDA Dockets Management Division on August 4, 2004, and subsequently assigned FDA Public Docket number 2004P-0349.

In the months since the submission of the Citizen Petition by the Coalition for Mercury-Free Drugs, scientific evidence has emerged to further link Thimerosal with serious adverse effects.

James et al. from the *University of Arkansas* and the *Food and Drug Administration* have reported in the peer-reviewed scientific/medical literature that the neurotoxicity of Thimerosal is associated with depletion of glutathione. The in vivo ethylmercury generated from the decomposition of Thimerosal binds to cysteine thiol (-SH) groups on intracellular proteins and inactivates their function. The cysteine-SH group of glutathione, binds mercury and protects essential proteins from functional inactivation. Glutathione is the major mechanism of mercury excretion, and individuals with genetic deficiencies in glutathione synthesis will be less able to excrete mercury and will be more sensitive to its adverse effects.<sup>1</sup>

James from the *University of Arkansas* has examined cysteine and glutathione plasma levels in children with autistic disorders in comparison to matched neurotypical children.<sup>2</sup> It was demonstrated that statistically significant reductions in plasma cysteine and glutathione were present in children with autistic disorders in comparison to the matched neurotypical children. Both, cysteine and glutathione, possess a strong ability to bind mercury at the -SH (thiol) site of cysteine. Hence, a decrease in cysteine and glutathione availability would be expected to

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<sup>1</sup> James SJ, Slikker W, Melnyk S, New E, Pogribna M, Jernigan S. Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors. *Neurotoxicology* (in press).

<sup>2</sup> James SJ. Impaired transsulfuration and oxidative stress in autistic children: Improvement with targeted nutritional intervention. Fall DAN!™ 2003 Conference, Portland, Oregon, 3-5 October 2003.

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negatively affect the ability to bind mercury in vulnerable sites, particularly the brain, and may have relevance to the neurological dysfunction observed in childhood neurodevelopmental disorders. In confirmation of the biochemical observations in autistic children, researchers have also analyzed genomic differences in autistic children in comparison to controls, and determined that there are statistically significant increased frequencies of single nucleotide polymorphisms (SNPs) for specific key functional enzymes within the glutathione synthesis pathway that would be expected to reduce the level of cysteine and glutathione present in autistic children.<sup>3</sup>

It has previously been widely reported that reduced/unusual pain sensitivity is a common feature of children with autism.<sup>4</sup> Jin et al. from the Department of Physiology and Biophysics, Seoul National University College of Medicine, have reported that TRPV1, a receptor for capsaicin, plays a key role in mediating thermal and inflammatory pain. Because the modulation of ion channels by the cellular redox state is a significant determinant of channel function, the researchers investigated the effects of sulfhydryl modification on the activity of TRPV1. Thimerosal, which oxidizes sulfhydryls, blocked the capsaicin-activated inward current (I(cap)) in cultured sensory neurons, in a reversible and dose-dependent manner, which was prevented by the co-application of the reducing agent, dithiothreitol. Among the three cysteine residues of TRPV1 that are exposed to the extracellular space, the oxidation-induced effect of Thimerosal on I(cap) was blocked only by a point mutation at Cys621. These results suggest that the modification of an extracellular thiol group can alter the activity of TRPV1. Consequently, the researchers concluded that such a modulation of the redox state might regulate the physiological activity of TRPV1.<sup>5</sup>

Researchers from *Northeastern University, Tufts University, Johns Hopkins University, and the University of Nebraska* have reported that methylation events play a critical role in the ability of growth factors to promote normal development. Neurodevelopmental toxins, such as ethanol and heavy metals, interrupt growth factor signaling, raising the possibility that they might exert adverse effects on methylation. The researchers determined that insulin-like growth factor-1 (IGF-1)- and dopamine-stimulated methionine synthase (MS) activity and folate-dependent methylation of phospholipids in SH-SY5Y human neuroblastoma cells, via a PI3-kinase- and MAP-kinase-dependent mechanism. The stimulation of this pathway increased DNA methylation, while its inhibition increased methylation-sensitive gene expression. It was determined that Thimerosal inhibited both IGF-1- and dopamine-stimulated methylation significantly at 1 nanomolar (0.0002 part-per-million [0.2 parts per billion] – levels considerably less than children receive from Thimerosal-containing childhood vaccines) concentrations and eliminated MS activity. The researchers concluded that their findings provide a molecular mechanism for how increased use of Thimerosal-containing vaccines may have contributed to the observed increase in autism and Attention-Deficit-Hyperactivity-Disorders (ADHD).<sup>6</sup> In addition, researchers have followed-up this previous work and shown that folate-dependent, phospholipid methylation in the

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<sup>3</sup> Boris M, Goldblatt A, Galanko J, James SJ. Association of 5,10-Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms with autistic spectrum disorders. *J Am Phys Surg* (in press).

<sup>4</sup> Tordjman S, Antoine C, Cohen DJ, Gauvain-Piquard A, Carlier M, Roubertoux P, Ferrari P. Study of the relationships between self-injurious behavior and pain reactivity in infantile autism. *Encephale* 1999;25:122-34.

<sup>5</sup> Jin Y, Kim DK, Khil LY, Oh U, Kim J, Kwak J. Thimerosal decreases TRPV1 activity by oxidation of extracellular sulfhydryl residues. *Neurosci Lett* 2004;369:250-5.

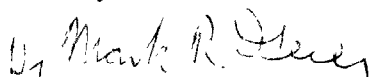
<sup>6</sup> Waly M, Olteanu H, Banerjee R, Choi SW, Mason JB, Parker BS, Sukumar S, Shim S, Sharma A, Benzecry JM, Power-Charnitsky VA, Deth RC. Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal. *Mol Psychiatry* 2004;9:358-70.

lymphoblasts of autistic children were significantly in a dose-response manner more sensitive to Thimerosal than in unaffected siblings.<sup>7</sup>

It is imperative that the FDA, which began to recommend removal of mercury from over-the-counter topical medicinal products over two decades ago, now immediately reduce mercury levels to trace amounts in all materials administered/injected/applied to children under the age of 3 and to pregnant women. In addition, since the manufacturers have repeatedly failed to prove the long-term safety of the mercury present in their drug products, these drug product makers must prove that the level of mercury in each drug is safe or, *failing that*, reformulate such products so that their mercury level is less than 3 parts per billion (0.0000003 %).

Finally, until all drug products contain no mercury above 3 parts per billion, drug products should be plainly labeled with their mercury level in parts per billion.

Thank you,



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<sup>7</sup> Deth RC, Waly M. How genetic risks combine with thimerosal to inhibit methionine synthase and cause autism. Fall DAN!™ 2004 Conference, Los Angeles, California, 1-3 October 2004.